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Trauma-Induced Insomnia: A Novel Model for Trauma and Sleep Research

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Summary

Traumatic events have been increasingly recognized as important precipitants of clinically significant insomnia. Trauma is an extreme form of stressful life event that generates a sustained neurobiological response triggering the onset and maintenance of insomnia. Trauma may disrupt the normal sleep-wake regulatory mechanism by sensitizing the central nervous system's arousal centers, leading to pronounced central and physiological hyperarousal. The central concept of hyperarousal has been linked to both the pathogenesis of insomnia and to the neurobiological changes in the aftermath of traumatic events, and may be a neurobiological commonality underlying trauma and

insomnia. This paper reviews evidence for trauma-induced insomnia and highlights its emergence as an important clinical and neurobiological entity. The production of insomnia by trauma may occur in the absence of full-blown PTSD, and may also be a precursor of subsequent PTSD development. Converging lines of evidence from the neuroscience of insomnia with the neurobiology and psychophysiology of stress, fear, trauma and PTSD will be integrated to advance understanding of the condition. Preclinical and clinical stress and fear paradigms have informed the neurobiological pathways mediating the production of insomnia by trauma. Elucidating the underlying neurobiological substrates can establish novel biological markers to identify persons at risk for the condition, and help optimize treatment of the trauma-insomnia interface. Early identification and treatment of insomnia in the posttraumatic period may prevent the development of PTSD, as well as other important sequelae linked to insomnia such as depression, substance dependence, and other medical conditions.

Keywords: trauma, insomnia, sleep disturbance, hyperarousal, PTSD, fear

Introduction

Insomnia is a prominent feature of the human neurobiological and physiological response to trauma. Following a traumatic event, exposed individuals report marked and enduring patterns of sleep disruption. That clinically significant insomnia (defined by symptoms of difficulty initiating sleep, difficulty maintaining sleep with sleep that is non-restorative, as well as awakening with difficulty returning to sleep) emerges in the aftermath of traumatic events has been increasingly established in sleep, trauma and stress research, and is a growing area of empirical focus [1].

This paper reviews the phenomenon of trauma-induced insomnia and highlights its emergence as an important clinical and neurobiological entity. The development of insomnia following a traumatic event may occur without the presence of full-blown Posttraumatic Stress Disorder (PTSD) as a specific, circumscribed consequence of trauma exposure. It is also an important predictor of PTSD development that may serve as an informative marker for subsequent PTSD severity. Moreover, trauma-induced insomnia may be a precursor of other disabling posttraumatic complications such as depression, substance dependence, and other impairing medical conditions [1,2]. The potential importance of targeted, early treatment of trauma-induced insomnia to the prevention of significant posttraumatic sequelae will be discussed.

The central concept of hyperarousal is hypothesized to be a pivotal mechanism linking the posttraumatic response to clinically significant insomnia [3]. Drawing from clinical, physiological, and neurobiological studies, the relevance of hyperarousal to the production of insomnia in the wake of trauma will be evaluated. Although an optimal animal model of the human response to trauma has not yet been developed, knowledge gleaned from animal models utilizing stress and fear paradigms that model important aspects of human traumatic responses has been fruitful [4,5]. Thus, preclinical stress and fear paradigms have the potential to inform the underlying neurobiological substrates of hyperarousal and insomnia posttrauma in humans, and the relevant findings will be discussed. The importance of establishing novel biological markers and optimizing treatments, and the need for prospective evaluation of trauma-induced insomnia with systematic studies, will be emphasized.

Insomnia and Traumatic Events

Chronic insomnia is a prominent and debilitating consequence of exposure to traumatic events. Trauma lies at the extreme end of a continuum model of stressful life events [6,7]. Traumatic events are defined formally in the DSM-IV as an event involving actual or potential death or serious injury that an exposed person experiences (or witnesses), and responds with intense fear, helplessness or horror [8].

The experience of a traumatic event can significantly disrupt sleep integrity and continuity in exposed individuals. Following the attacks of September 11, 2001, approximately 25% of New Yorkers suffered from clinically significant insomnia [9]. Survivors of traumatic events, including natural disasters, motor vehicle accidents (MVA)'s and industrial accidents, routinely exhibit marked sleep disruption, specifically longer latency to sleep onset, markedly increased nocturnal awakenings, and decreased global ratings of sleep quality compared to before the traumatic event [10]. The greater the degree of exposure to the traumatic event has been shown to be related to greater distress and symptomatological impact post-trauma [11].

Varela et al [12] investigated the psychological impact of the September 7, 1999 earthquake in Athens one year after the event in 305 exposed individuals. The main consequence was sleep disturbance, with 54% of the subjects experiencing significant sleep problems. Within this group, 90% experienced clinically significant insomnia, and 25% reported nightmares. The degree of stress and perception of lack of control after the earthquake was a significant predictor of the resultant insomnia.

Askenasy and Lewin [13] surveyed individuals during missile attacks in the Gulf war and followed them after the war was over. 38% of the sample developed acute insomnia

that persisted for several months after the attacks. Lavie et al [14] found that missile attacks during the Gulf War resulted in significantly increased nighttime awakenings in a random sample of 200 Israeli adults and children, compared to the incidence of sleep disturbance in a sample of Israeli industrial workers in 1981. Taken together, these studies demonstrate that traumatic events are important precipitants of clinically significant insomnia.

Moreover, insomnia often emerges after a severe traumatic event independent of the development of PTSD. McMillen et al [15] interviewed 130 survivors of the 1993 Northridge California earthquake and found that, at 3 months, 13% of the sample met full criteria for PTSD. However, 48% of the otherwise psychiatrically healthy sample met full criteria for the hyperarousal and reexperiencing symptom clusters, and the most prevalent hyperarousal symptoms were sleep disturbance and exaggerated startle. Further, insomnia may differentially co-occur with symptoms of the hyperarousal cluster, and not the other symptoms clusters (ie. emotional numbing, behavioral avoidance) that are manifested in full blown PTSD. Importantly, comorbidity with PTSD or any other psychiatric conditions that existed prior to the earthquake was associated only with those subjects reporting avoidance and numbing (cluster C) and poor concentration (cluster D) following the earthquake, and not hyperarousal.

The significant insomnia and startle that emerged following earthquake exposure were those most closely linked to fear and stress responses that may be acutely activated following exposure to a traumatic event [16]. Interestingly, in this study nightmares were not present in the acute posttraumatic period. It is possible that nightmares may emerge after a longer interval of time where more complex emotional processing of the traumatic

event has had the opportunity to occur [17], whereas insomnia may be proximally linked to, and a more immediate consequence of, acute trauma exposure [15]. However, this is not supported by other studies showing that nightmares also manifest in the immediate aftermath of trauma, and that peritraumatic nightmares often resolve (18,19).

Lewis et al [20] found similar reports of sleep disturbance in war veterans without PTSD compared to those with PTSD. 100% of PTSD veterans and 90% of non-PTSD veterans had significant disturbances in sleep. Although the majority of sleep measures were more severe in the PTSD group, there were no differences in sleep efficiency between the non –PTSD and PTSD groups. That is, sleep efficiency was not *more* impaired in the PTSD group compared to the non-PTSD group. Importantly, 67% of the non-PTSD veteran group had sleep quality scores in the severely impaired range. Exposure to combat related traumatic events in both groups, independent of the presence of formal PTSD, may have contributed to their comparable frequency of sleep impairment. Similarly, North et al [21] found that after the Oklahoma City bombing, approximately 70% of 182 adults exposed reported clinically significant insomnia, and hyperarousal symptoms were the most common overall.

In summary, traumatic events have been shown to be important precipitants of insomnia in exposed individuals. The acute emergence of insomnia in the aftermath of trauma can lead to sustained disruptions in sleep continuity and restorative efficacy. Trauma- induced insomnia may occur in the absence of full-blown PTSD. Finally, insomnia induced by a traumatic event often differentially co-occurs with other symptoms of hyperarousal.

Insomnia and PTSD

The development of insomnia following traumatic events has also been demonstrated to be a constitutive element of PTSD. Sleep disturbance is a fundamental and enduring complaint of PTSD patients and has been considered the hallmark of the disorder [17, 22]. Studies on PTSD have documented significant subjective sleep complaints [23, 24]. Further, a 3 month prospective study found that insomnia was the most frequently reported symptom and predicted the other symptom clusters of PTSD in a group of war veterans [25]. Disruptions in total sleep time and sleep efficiency are the subjective parameters most specifically associated with PTSD [26].

Objective polysomnographic studies of sleep disturbance in PTSD have produced mixed results [27-30]. This has been attributed to a large number of secondary factors confounding sleep study, such as considerable heterogeneity in samples across studies with respect to age, sex, time elapsed since trauma, and presence of psychiatric comorbidity [31, 32]. The majority of studies have focused on the chronic phase of the disorder, and not its acute phase [33]. Numerous studies suggest PTSD patients may overestimate their actual sleep disruption, though a recent meta-analytic study found that PTSD patients actually underestimated sleep problems, and that the discrepancies between subjective and objective sleep reports in PTSD have been overstated [34].

Despite the mixed findings, a regularly observed PSG pattern in PTSD is evidence for increased arousals, awakenings and sleep fragmentation patterns. A large epidemiological study of sleep in PTSD identified significantly increased arousals from REM sleep as objectively measured by PSG [35]. Similarly, Germain and Nielsen [36] studied objective sleep measures in 9 PTSD nightmare sufferers and 11 idiopathic nightmare

sufferers, and found that the PTSD group exhibited overall poorer sleep efficiency secondary to significantly increased nocturnal awakenings compared to the non-PTSD group.

Consistent with these findings, a meta-analysis of objective PTSD sleep abnormalities found that, controlling for relevant confounds, PTSD subjects exhibited overall more stage 1 (ie, less restorative) sleep and less slow wave (deep) sleep and increased REM density compared to non-PTSD subjects [34]. Increased REM density may be linked to subtle and persistent REM fragmentations in PTSD [37, 38]. REM instability has been hypothesized to account for the experience of non-restorative sleep and for the discrepant results across studies [39, 40].

In summary, insomnia is an important part of the diagnostic picture of PTSD. A pattern of increased arousals, awakenings and fragmentation of both non-REM and REM sleep can be gleaned from the available polysomnographic data in PTSD, despite ambiguities and inconsistencies across studies. A potential pathogenic mechanism for this pattern is increased central hyperarousal following the traumatic event.

Objective Measures of Sleep Disturbance Following Exposure to Traumatic Events

The objective measurement of sleep disturbance in the aftermath of trauma is an understudied area. The available polysomnographic studies point to significant abnormalities in sleep measures following traumatic events, and corroborate the findings of increased insomnia prevalence in the posttraumatic period.

Mellman et al [41] evaluated sleep disturbance and its relation to major psychiatric sequelae within a year of Hurricane Andrew. The study subjectively assessed sleep

function in 54 hurricane victims and objectively evaluated PSG in a subgroup of 10 hurricane victims compared to nine subjects who were unaffected by the hurricane. For the hurricane victims, objective sleep reports demonstrated significant and trend significant differences for arousals per hour, and microawakenings, as well as increased entries into stage 1 sleep, the lightest stage of sleep that serves as a transition to more restorative stages, but has limited restorative capacity itself. Importantly, the hurricane victims were unable to attenuate their arousal levels during sleep. Arousal attenuation is a key determinant of non-fragmented deep sleep**.** In addition, the PSG findings in the posttraumatic period were correlated with the subsequent development and maintenance of PTSD.

Hefez et al [42] studied a sample of 11 trauma survivors and found significant effects of trauma exposure on sleep architecture compared to controls. Historical control data of age matched normal non-traumatized men from a different study were utilized. Three types of traumatic events were documented: holocaust, combat, and sea disaster. All survivors displayed shorter REM, fragmented REM, longer REM latency, and increased awakenings compared to the control data. Subjects assessed at time points closer to the traumatic event displayed more objective PSG abnormalities than those at more delayed times.

Distal trauma also relates to objective measures of insomnia and sleep disturbance. Bader et al [43] demonstrated a link between early trauma with physiological markers and clinical symptoms of adult primary insomnia. 46% of 59 adult primary insomniacs reported moderate to severe adverse childhood events (ACEs) measured by the Childhood Trauma questionnaire. Accordingly, this group (moderate to severe ACE)

displayed a greater frequency of nighttime awakenings and more movement arousals compared to the low or no ACE group. Further, actigraphy confirmed more disturbed sleep and increased nocturnal activity for the high ACE group compared to the low ACE group. The high ACE group also had a slightly greater increase in salivary cortisol in response to induction of either positive or negative memories, suggesting sensitized stress system responsivity secondary to ACEs that may be relevant to sustained frequency of nocturnal awakenings. That adverse childhood experiences can influence subsequent adult stress responsivity has been demonstrated [44] and has implications for the development and maintenance of chronic insomnia [45].

In summary, there is emerging evidence for objective measures of sleep disruption following a traumatic event. Further, trauma exposed individuals manifest sleep fragmentation patterns consistent with an underlying mechanism of hyperarousal.

Trauma-Induced Insomnia as a Risk Factor for PTSD Development

Although prospective studies are limited, the available evidence suggests the emergence of clinically significant insomnia following exposure to a traumatic event has important implications for the subsequent development of PTSD. Koren et al [46] prospectively examined the longitudinal course of sleep disturbance in 102 motor vehicle accident (MVA) survivors and 19 controls at 1 week, and 1, 3, 6 and 12 months posttrauma. The control group was a demographically matched group of 19 patients hospitalized in the same unit for elective surgery. MVA survivors were grouped into those with PTSD and without PTSD. After one month, clinically significant insomnia emerged that differentiated the PTSD from the non-PTSD group. This difference was

sustained and widened over the first 3 months, then stabilized from 3 to 12 months, as the non-PTSD MVA survivor group insomnia normalized. The results of this study suggest that it may be possible to predict the eventual emergence of PTSD on the basis of insomnia complaints by one month posttrauma. This has important implications for treatment, and suggests that early effective amelioration of insomnia can impede or prevent full blown PTSD development in trauma survivors.

Wright et al [47] prospectively evaluated 659 active duty soldiers that were assessed at both 4 months and 8 months after return from a 12-month long deployment in Iraq. Clinically significant insomnia at the 4 month point was a strong predictor of PTSD and depression symptoms at the 12 month follow up. By contrast, PTSD and depression at 4 months were not significant predictors of insomnia. Additionally, insomnia at time 1 predicted the emergence of intrusive memories at time 2, but not vice versa. This may suggest that insomnia can trigger the development of more generalized fear responses manifested by intrusive memories, underscoring that insomnia in the posttraumatic period may be a critical antecedent of later psychopathology.

REM fragmentation in the acute posttraumatic period may be an important predictor of PTSD development. Mellman et al [48] contrasted PSG findings in recently injured and hospitalized patients both near the time of initial trauma and at one month posttrauma, and prospectively assessed the development of PTSD. The main finding was significantly shorter duration of continuous REM (or significantly increased fragmented REM sleep) in the group that developed PTSD than the group that did not develop PTSD. Further, discontinuity of REM sleep was significantly negatively correlated with PTSD symptom severity. REM sleep disruption is an important objective correlate of clinical

insomnia [40], and its emergence in the posttraumatic period may predict the subsequent development of PTSD and correlate with the degree of symptom severity expressed.

Sleep disruption following trauma predicted the subsequent later development of PTSD, and may have differential predictive power for female trauma survivors. Kobayashi et al [49] examined sleep and PSG data in the early aftermath of trauma in 13 female and 22 male trauma survivors with no prior history of PTSD. Traumatized women who eventually developed PTSD had significantly greater impairment in sleep maintenance and significantly reduced TST than those who did not develop PTSD. Further, the women with subsequent PTSD had a greater wake after sleep onset (WASO) than the male subgroup that developed PTSD. However, both males and females with subsequent PTSD had shorter duration of REM sleep segments, and an increased number of REM sleep segments posttrauma than subjects who did not develop PTSD.

The emergence of clinically significant insomnia in the wake of trauma may also influence the development of other important psychiatric sequelae, including alcohol and drug abuse and dependence, major depression [47]. This is an understudied area that is an important focus of future research on trauma-induced insomnia.

In summary, insomnia induction following trauma has implications for the development of subsequent psychopathology. Importantly, traumatized individuals who manifest insomnia in the peritraumatic period are at greater risk for developing PTSD than individuals who do not experience insomnia.

The Central Concept of Hyperarousal: Neurobiological Convergence of Trauma and Insomnia

The pathogenic mechanisms mediating trauma-induced insomnia are not fully understood but have been partially elucidated by emerging research in trauma, stress and sleep neurobiology and psychophysiology. The impact of a traumatic event mobilizes a vigorous stress/fear response that manifests as central and peripheral hyperarousal [50]. Hyperarousal in specific interconnecting brain areas (reticular activating system, amygdala, and prefrontal cortex) may be a critical component of the pathogenic mechanism necessary to develop and maintain chronic insomnia [37, 51, 52].

The human response to trauma has been conceptualized as an intense stress/fear reaction that involves robust activation of central and peripheral physiological arousal systems [16]. Trauma may generate an intense, sustained hyperarousal state by activating the amygdala, a key limbic system structure that has been shown to be critical to subserving stress and fear responses [53]. Amygdala activation, in turn, kindles heightened arousal in the brainstem, promoting activation and alertness, as well as more complex cognitive and emotional hyperarousal [54]. Generalized activation of arousal systems may function to develop and maintain clinically significant insomnia in the posttraumatic period, and insomnia induced by trauma may involve an amplification and exaggeration of the generalized hyperarousal mechanism underlying primary insomnia. Thus, the central concept of hyperarousal may be critical to determining how traumatic events are linked with the induction of insomnia.

Hyperarousal and Insomnia

Hyperarousal has been demonstrated to be a dominant pathophysiological mechanism underlying primary insomnia [55, 56]. Patients with insomnia consistently display signs of central and peripheral arousal and activation that correlates with sleep impairment. The evidence for the concept of hyperarousal to the pathogenesis of insomnia has been comprehensively reviewed [51, 38]. Further, individuals with a genetic vulnerability to hyperarousal may be more likely to develop disrupted sleep [57].

The hyperarousal model of insomnia suggests that hyperactivation of central arousal centers and increased sympathetic activity contribute to a generalized state of neurobiological and physiological arousal that interferes with sleep onset, continuity, and overall restorative efficacy. The majority of studies demonstrate that subjects with insomnia have increased secretion of the Hypothalamic-Pituitary-Adrenal (HPA) axis and the sympathetic nervous system, the two key limbs of the stress response [58, 45]. Studies have demonstrated exaggerated reactivity of arousal mechanisms in insomniacs versus normal sleepers over a wide range of psychophysiological measures, including heart rate variability, whole body metabolic rate, central and peripheral stress hormones, experimentally induced sympathetic activation with caffeine, and evoked and spectral EEG measures [55, 59, 60, 61, 62].

Overall, individuals with high levels of baseline arousal tend to have interrupted or fragmented sleep. That baseline arousal level may be a partially genetically determined physiological trait has been supported by several studies. Further, the vulnerability and sensitivity of trait or basal arousal level to external environmental cues that is relevant to the mechanism of trauma-induced insomnia, may also be partially inherited [63].

The neurobiological and psychophysiological evidence for hyperarousal has been corroborated with neuroimaging studies. Nofzinger et al [56] investigated central brain mechanisms in 7 subjects with insomnia and 20 healthy controls. Insomnia subjects showed greater global cerebral glucose metabolism during sleep and while awake than control subjects. This study suggests insomnia may be a failure of arousal mechanisms to attenuate normally during sleep. That is, a hyperactive arousal system may carry over from waking to sleep states, promoting a sustained state of hyperarousal that maintains clinically significant insomnia.

In summary, substantial evidence exists for central hyperarousal as a critical neurobiological substrate of insomnia. This overlaps with a state of hyperarousal that is hypothesized to occur following a traumatic event.

Symptomatic Hyperarousal in the Posttraumatic Period

If a state of generalized hyperarousal is activated following a traumatic event, hyperarousal symptoms should be prominent in the posttraumatic period, and also may predict the development of PTSD. Accordingly, Schell et al [64] found in a large sample of adult survivors of community violence that hyperarousal following trauma was the strongest predictor of the longitudinal course of subsequent PTSD symptom severity, and was the symptom cluster that most significantly influenced the progression over time of the other PTSD symptom clusters of emotional numbing and avoidance. When assessing

the relative contributions of the three symptom clusters to the development and course of overall PTSD severity, hyperarousal also emerged as the most important predictor. Similarly, a prospective study of 264 orofacial injury survivors using cross-lagged path analysis found that postinjury hyperarousal was the best prospective predictor of the other symptom clusters of PTSD while controlling for the possible influence of the other symptom clusters. Importantly, neither reexperiencing or avoidance influenced scores on the other clusters over time, by contrast with hyperarousal. Thus, hyperarousal has a key role in the temporal progression of posttraumatic psychological effects [65].

Importantly, Schell et al [64] also found that insomnia and startle may be differentially more strongly associated with the development of PTSD than other hyperarousal symptoms. This further suggests that hyperarousal is not a unitary construct, but may encompass symptoms with different underlying mechanisms. That is, insomnia and concentration, though formally subsumed under the dimension of hyperarousal, may represent separate pathogenic processes that independently impact subsequent PTSD development.

Heir et al [66] found in a sample of 899 Norwegian survivors of the 2004 Tsunami disaster that at 6 months after the trauma, hyperarousal symptoms were more closely linked to functional impairment than other symptom clusters. The level of hyperarousal in the aftermath of trauma was most closely related to the degree or severity of trauma exposure. North et al [21] reported that approximately 80% of survivors of the Oklahoma City Bombing experienced several hyperarousal symptoms including insomnia, exaggerated startle, and poor concentration. Naifeh et al [67] further suggested that hyperarousal symptoms may result from distinct and specific trauma exposure, whereas

other PTSD symptoms such as negative affect and emotional numbing may be a consequence of less well defined or circumscribed trauma.

That the experience of a traumatic event may induce activation of a central mechanism of hyperarousal is reinforced by the emergence of panic attacks in the posttraumatic period. Individuals with PTSD from the NCS were analyzed for patterns of comorbidity in relation to prevalence of sleep disturbance. The comorbidity between PTSD and panic disorder demonstrated significantly higher complaints of insomnia (as well as nightmares) compared to any other comorbidity, including major depression [68]. The emergence of panic attacks posttrauma has been shown to be one of the strongest predictors of subsequent PTSD development [69]. Non-respiratory panic attacks occurring with PTSD may be amplified states of hyperarousal that act synergistically with generalized neurobiological arousal posttrauma, magnifiying the hyperarousal and more readily inducing insomnia.

In summary, there is significant evidence that clinical symptoms of hyperarousal emerge in the posttraumatic period. This reinforces the concept of generalized central hyperarousal that is hypothesized to occur following trauma, and that may underlie trauma-induced insomnia.

Physiological Hyperarousal in the Posttraumatic Period

If hyperarousal symptoms are induced and prominent posttrauma, it follows that there should be concomitant objective, measureable activation of neurobiological arousal systems in the posttraumatic period [70]. Emerging evidence demonstrates that significant physiological arousal occurs following a traumatic event. Moreover, excessive

physiological activation posttrauma may be one of the central pathogenic determinants of subsequent PTSD development [71, 72].

Shalev et al [73] measured indices of sympathetic activation in eighty six trauma survivors upon admission to the emergency department and 1 week after trauma. Subjects who developed PTSD had significantly higher heart rates than those who did not develop PTSD. Robust physiological arousal posttrauma may play a central role in the pathogenesis of PTSD. Specifically, arousal following trauma may mediate a conditioned fear response that contributes to persistent PTSD symptoms.

Similarly, Bryant et al [74] demonstrated that the level of acute hyperarousal in the posttraumatic period contributes to the development of PTSD. They investigated 146 hospitalized MVA survivors and assessed for acute stress disorder 1 month after trauma and for PTSD 6 months after trauma. Subjects who developed PTSD had higher heart rates upon discharge than those who did not develop PTSD, suggesting that the development of PTSD is strongly mediated by arousal level in the acute posttraumatic period. This finding also extends to children; Kassam-Adams et al [75] found in a large scale prospective study that traumatically injured children (aged 8-17) who developed partial or full PTSD had a higher mean heart rate acutely following the trauma than those who did not develop PTSD. Importantly, within the subthreshold group, the elevated HR group, compared to the non-elevated HR group, was more likely to meet criteria specifically for the hyperarousal symptom cluster, and not the avoidance or reexperiencing clusters. Other studies, however, have failed to show a relationship between increased heart rate in the acute posttraumatic period and subsequent PTSD development [76, 77].

Those prone to develop hyperarousal posttrauma may exhibit abnormal function.of GABA, the main inhibitory transmitter system in the CNS that modulates excessive HPA axis activation during acute stress and fear responses. Vaiva et al [78] measured plasma GABA levels in 108 MVA victims in the immediate posttraumatic period. Subjects with lower mean GABA levels were more likely to be diagnosed with PTSD at 6 weeks posttrauma than those with higher GABA levels. Low or abnormal GABA may result in decreased inhibition of the HPA axis and central adrenergic activity, allowing both systems to reach a higher intensity posttrauma, and then act relatively unopposed over a prolonged period of time. Low GABA has been linked to the pathophysiology of primary insomnia [79], and may contribute to hyperarousal and the emergence of insomnia posttrauma.

If physiological hyperarousal occurs after trauma and predicts PTSD, targeting arousal systems with pharmacological treatment should impede PTSD development. Prazosin is an alpha-adrenergic blocker that functions to decrease sympathetic activity and attenuate excessive arousal. In controlled studies, prazosin reduced symptoms of insomnia as well as nightmares [80], and normalized objective measures of sleep disturbance [81]. Although a nascent area, the development and identification of pharmacological agents that decrease hyperarousal should be an important emphasis of future research [82].

In summary, evidence suggests that a state of physiological hyperarousal is activated following a traumatic event. This physiological hyperarousal is associated with increases in CRH activity and reductions in GABA, and predicts the later development of PTSD. Physiological hyperarousal is also correlated with increased sleep fragmentation and decreased sleep efficiency in the posttraumatic period.

Posttraumatic Hyperarousal and Sleep Measures

If a state of hyperarousal is a critical determinant of sleep disruption posttrauma, indices of hyperarousal should be correlated with increased sleep fragmentation and decreased sleep efficiency in the posttraumatic period. The available evidence suggests posttraumatic hyperarousal is linked to objective measures of sleep disturbance.

Mellman et al [83] examined physiological hyperarousal and its relation to sleep in the acute posttraumatic period. Peripheral sympathetic nervous system activation during sleep was assessed by measuring heart rate variability in subjects recently exposed to a traumatic event within one month of the trauma. The nine subjects that went on to develop PTSD had significantly increased sympathetic activation during REM sleep compared to ten exposed subjects that did not develop PTSD. Interestingly, inspection of the subject profiles reveals that one third of the group categorized as PTSD did not meet full criteria for the disorder, but actually had subclinical disorder meeting full criteria for the hyperarousal and re-experiencing symptom clusters.

Important interrelationships between HPA axis hyperarousal and sleep measures have been demonstrated in the context of trauma. Otte et al [44] demonstrated in 20 male PTSD subjects that increased 24 hour urinary cortisol, likely reflecting increased Corticotropin Releasing Hormone (CRH) drive, was significantly negatively correlated with amount of delta sleep or time spent in delta sleep measured by PSG. Delta sleep time is an important marker of normal sleep regulation that is closely associated with the restorative capacity of sleep. CRH is hypothesized to stimulate locus ceruleus activity, increasing overall arousal levels that negatively impacts delta sleep integrity [84].

Similarly, van Liempt et al [85] found that PTSD patients exhibited increased ACTH levels and heart rate during sleep compared to healthy controls, and the ACTH increases correlated with increases in nighttime awakenings. Both ACTH and cortisol levels were inversely related to time spent in slow wave sleep measured by objective polysomnography.

Central hyperarousal measures are also correlated with sleep measures in PTSD. Fifty six unmedicated non-apneic combat veterans with PTSD were compared to healthy controls utilizing spectral power analysis of sleep EEG [70]. Low frequency EEG power during slow wave sleep was significantly reduced in the patient group, indicative of greater central hyperarousal. Importantly, there was a direct correlation between the NREM power and clinical hyperarousal scores measured on the CAPS. Interestingly, heart rate during sleep was not increased in the PTSD group, suggesting that a heightened central hyperarousal state may at times be uncoupled with concomitant physiological activation in chronic PTSD.

Modelling the Link Between Posttraumatic Hyperarousal and Insomnia Using Experimental Stress Induction and Stress Measures

Experimentally modeling the link between trauma-induced hyperarousal and sleep disturbance is an emerging research area. Since traumatic events are at the extreme end on a continuum of severity with stressful events, studies utilizing stress paradigms and stress measures may inform the physiological substrates of trauma-induced insomnia.

In humans, experimental induction of psychological stress with an established stress paradigm demonstrated a close interrelationship between stress exposure, physiological

hyperarousal, and sleep disruption. Psychological stress was closely linked to levels of physiological arousal during NREM sleep, and higher levels of perceived stress correlated with lower levels of delta sleep in human subjects [86].

Drake et al [87] examined factors modulating vulnerability to the experience of transient sleep disruption. Individuals with higher scores on the Ford Insomnia Response to Stress Test (FIRST) had significantly lower sleep efficiency and increased latency to stage 1 sleep compared to subjects with lower FIRST scores. These subjects had elevated sleep latency measured by the Multiple Sleep Latency Test, indicating greater physiological arousal compared to subjects with low FIRST scores. This difference persisted after controlling for current and past insomnia. Overall, the study supports that a stress related vulnerability to sleep disturbance is mediated by increased physiological hyperarousal.

Garde et al [88] found strong bi-directional associations between psychological arousal, stressful events, and sleep quality in a large sample of healthy individuals. Overall, increased psychological arousal measured by the Stress-Energy Inventory (SEI) was positively correlated with poor subjective sleep reports. Further, negative events during the day, and bedtime stress ratings, were linked to poorer sleep quality. By contrast, arousal related to positive life events (compared to negative or stressful life events) was not associated with poor sleep. Contrary to predictions, however, salivary cortisol was not associated with arousal or sleep. This may have been due to the lack of a specific stress induction paradigm, as well as utilizing a sample of only healthy individuals.

Potential Neurobiological Substrates of Trauma-Induced Insomnia: Preclinical and Clinical Models

The acute response to a traumatic event involves significant activation of fear and stress systems, leading to a surge in arousal and vigilance that may underlie the production of insomnia following trauma [89]. The neurocircuitry of acute fear and stress responses has been predominantly informed by preclinical models of unconditioned and conditioned fear, as well as stress paradigms [90, 4]. A traumatic event serves as an unconditioned stimulus that evokes an immediate arousal and fear (unconditioned) response in exposed individuals. An exaggerated, sustained state of central hyperarousal is then activated that continues to be manifested after the initial fear reaction [91]. Therapeutic agents given early posttrauma that target sympathetic hyperarousal, such as propranolol, may function to decrease conditioned fear and thereby impede PTSD development [92]. The degree of the initial fear response can predict the later development of fear and avoidance generalization seen in PTSD both in humans [93] and in preclinical PTSD models [94].

Extensive preclinical work has identified the amygdala as a critical mediator of arousal and fear responses induced by a traumatic event [54, 95]. The amygdala is at the center of a well delineated neural network that subserves fear and anxiety in preclinical paradigms, and anxious states across a range of clinical disorders [96]. Acutely stressful contexts in humans induce a highly sensitized state in the amygdala that responds more robustly and nonselectively to a broad range of stressful stimuli [97]. Overall, there is substantial evidence that the amygdala plays a central role in the processing of and responsivity to

emotionally stressful stimuli. Of specific relevance to trauma is amygdala activation of hyperarousal linked to insomnia and sleep disturbance [98].

The amygdala reciprocally connects with key brain areas that regulate the HPA axis, cardiovascular responses, and respiratory activity, all of which are activated during heightened arousal and fear [99]. Reciprocal connections to the locus coeruleus are critical to generating norepinephrine release that mediates central hyperarousal following stress [100, 101]. The amygdala has also been extensively implicated in the modulation of arousal and regulation of sleep [102]. The amygdala is ideally situated anatomically to stimulate the reticular activating system. Such stimulation is dependent upon the specific emotional state generated by the amygdala. The major descending output of the amygdala projects via the central nucleus to brainstem regions considered central to the control of REM and other sleep stages as well as PGO wave generation [103].

In the aftermath of acute stress the amygdala increases hyperarousal, vigilance and threat detection by enhanced and prolonged functional connectivity to the dorsal anterior cingulated cortex (DACC) and anterior insula (AI) [104]. Resting state combat- related PTSD patients display enhanced amygdala-insula connectivity that may indicate a heightened and pervasive hyperarousal state [105]. Emerging evidence suggest patients with insomnia also display abnormalities in amygdalar connectivity to key brainstem and limbic areas that overlaps with the stress and PTSD findings [106].

The hippocampus also subserves generalized and cued fear responding [90]. Further, hyperarousal secondary to amygdala activation in fear states may result in hippocampal atrophy [107], leading to impaired extinction of learned fear. Abnormalities in hippocampal size and function are linked to impairment in PTSD, and may be

specifically relevant to insomnia posttrauma. Importantly, primary insomnia is similarly linked to smaller volumes of the hippocampus [108]. However, Winkelman et al [109] did not find evidence of decreased hippocampal size in primary insomniacs. The potential role of hippocampal abnormalities in insomnia is an important area of future investigation.

In a combined sample of war veterans both with and without PTSD, increased severity of insomnia was associated with smaller volumes of the CA3/dentate subfields of the hippocampus. Importantly, insomnia was more strongly associated with hippocampal volume than total PTSD symptom severity, reinforcing insomnia as a core posttraumatic feature important to developing and perpetuating full blown PTSD. An important implication of this study is that successful treatment of insomnia early posttrauma may prevent hippocampal degeneration, leading to increased hippocampal volume and potentially impeding PTSD development [110].

The conditioned fear paradigm is relevant to the underlying neurobiology of insomnia and sleep disturbance following trauma. Successful extinction of contextual fear in rodents normalizes sleep disturbances that emerge after shock training and fear elicitation [111], and fear conditioning was shown to specifically fragment sleep architecture in rats [112-114].

In humans, sleep disruption promotes sustained states of conditioned fear; conversely, sleep integrity facilitates its extinction. For example, fear conditioning was contrasted before and after either 12 hours of waking, or 12 hours of a normal nights sleep, using skin conductance as the conditioned response [115]. A previously unextinguished conditioned response was more readily extinguished after the sleep condition than the

wake condition. Insomnia induced by a traumatic event may maintain resultant conditioned fear responses resistant to extinction, and this may be an important mechanism whereby insomnia posttrauma contributes to the generalization of fear responding characteristic of full blown PTSD [115, 116]. Spoormaker et al [117] determined that the extinction of conditioned fear responses to shock exposure was impaired in subjects without REM sleep compared to subjects who had REM sleep, and this impaired extinction correlated with less activity in the left ventromedial prefrontal cortex, an important area mediating extinction learning [118].

The specific neural circuitry underlying sleep perturbations induced by stress and fear states in preclinical models is an emerging neuroscience area that may elucidate substrates of trauma-induced insomnia in humans. Rodent studies suggest administration of intense stressors models the human stress response and leads to prolonged disruptions in sleep architecture [119].

Cano et al [120] exposed rats to a specific psychological stressor (cage exchange) that causes an acute stress response associated with autonomic and HPA axis activation, and later generates an objective pattern of sleep disturbance seen in stress induced insomnia in humans, including increased sleep latency, decreased and fragmented non-REM and REM sleep, and high frequency EEG activity during non-REM sleep. That this paradigm produces sleep perturbations that are sustained after cessation of stressor exposure (and not simply parallel to an ongoing stressful context) suggests it may be an effective model of trauma-induced insomnia.

Further, in this study the emergent sleep disturbance patterns were associated with unique activation of specific arousal, limbic and cortical systems, specifically the central

nucleus of the amygdala and the bed nucleus of the stria terminalis that provide input to arousal areas, as well as the tuberomamillary nucleus and locus ceruleus areas, and involved increases in norepinephrine activity. Importantly, only CeA and BST lesions, but not LC lesions, restored REM sleep, implicating LC independent areas in hyperarousal activation [120]. Consistent with these findings, Liu et al [121] found that CRF receptor antagonism in the central nucleus of the amygdala differentially reduced fear-induced disruptions in REM sleep and neuronal measures of increased arousal.

Taken together, the combined preclinical and clinical studies have begun to formulate a putative neurobiological map of the trauma-insomnia interface. An emerging area in preclinical work is the development of models that may specifically inform sleep disruption in the acute posttraumatic period. Continued expansion of the findings of Pace-Schott et al [115] and similar human studies will likely prove fruitful.

INSERT FIGURE 1 HERE

Future Directions: Implications for Novel Biological Markers, Therapeutic Interventions, and Need for Prospective Studies

Biological markers of trauma-induced insomnia can help to identify individuals at high risk for the condition. The primacy of hyperarousal in the disorder's pathogenesis suggests the neurobiological substrates of posttraumatic hyperarousal can provide an important avenue for novel biomarker research [83]. Early identification of affected

individuals may lead to earlier and more effective treatment that can lessen the impact and associated sequelae of insomnia posttrauma.

The continued development of targeted pharmacologic and non-pharmacological treatments for trauma-induced insomnia is critical for the amelioration of symptoms as well as prevention of full-blown PTSD. Systematic research that characterizes the objective sleep abnormalities associated with trauma-induced insomnia is necessary. Prospective studies are needed to more fully delineate the natural history of trauma-induced insomnia and determine the relevant morbidities. Particular focus should be placed on elucidating how trauma-induced insomnia increases vulnerability to other impairing psychiatric and medical conditions such as depression and substance dependence**.** Finally, prospective research that identifies the patterns of response of trauma-induced insomnia to treatment, and that determines the polysomnographic correlates of these response patterns, are understudied areas that will be highly informative.

Summary

Diverse lines of research have demonstrated that clinically significant insomnia is an important consequence of exposure to traumatic events. Trauma-induced insomnia is a highly prevalent, disabling and underrecognized phenomenon, and its optimal management is poorly understood at present. That insomnia in the wake of trauma may occur without the presence full-blown PTSD, and is an antecedent of complicated

posttraumatic sequelae such as PTSD, substance dependence, and other medical conditions, highlights its importance as a clinical phenomenon and as a pathogenic marker of subsequent disability. The accumulated neurobiological and psychophysiological evidence points to central hyperarousal as the primary substrate of trauma-induced insomnia. This has implications for elucidating the relevant neuroanatomical and neurochemical pathways that can inform the development of targeted pharmacotherapeutic treatments, as well as the potential establishment of novel biological markers for the condition.

The author reports no conflicts of interest.

Practice Points

It is important to recognize:

1. Clinically significant insomnia is an important and debilitating consequence of exposure to traumatic events.

2. The central concept of hyperarousal is critical in understanding the pathogenesis of trauma-induced insomnia

3. Trauma-induced insomnia is an important precursor of PTSD development

Research Agenda

1. The objective sleep correlates of trauma-induced insomnia need to be systematically studied further, as well as the natural history of the condition.

2. The optimal pharmacotherapeutic management of trauma-induced insomnia is an important research focus that will aid in preventing morbidity.

3. The development of novel biological markers that build on the neuroscience of hyperarousal is critical to advancing early detection of trauma-induced insomnia

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Figure 1. Hypothetical Model of Trauma-Induced Insomnia